بسم الله الرحمن الرحيم

In The Name Of ALLAH

The Most Gracious, The Most Merciful

Armed Forces College of Medicine

AFCM

Antidepressant drugs

Prof. Dr/ Omayma Khorshid

INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture you will be able to:

Lecture 1

1. List the drugs used in treatment of depression.
2. Describe the probable mechanisms of action and the major characteristics of TCAs, including receptor interactions, adverse effects (from chronic use and in overdose) and clinical uses.

Lecture 2

3. Explain the limited role of MAO inhibitors in affective disorders.
4. Identify the drugs classified as SSRIs and SNRIs, and describe their characteristics, including clinical uses, adverse effects, toxicity, and potential drug interactions.

Antidepressant Drugs

Depression

A psychiatric disorder characterized

- Intense feelings of sadness, hopelessne

- Loss of interest in usual activiti

- Diminished ability to experience pleasu in usual activities .

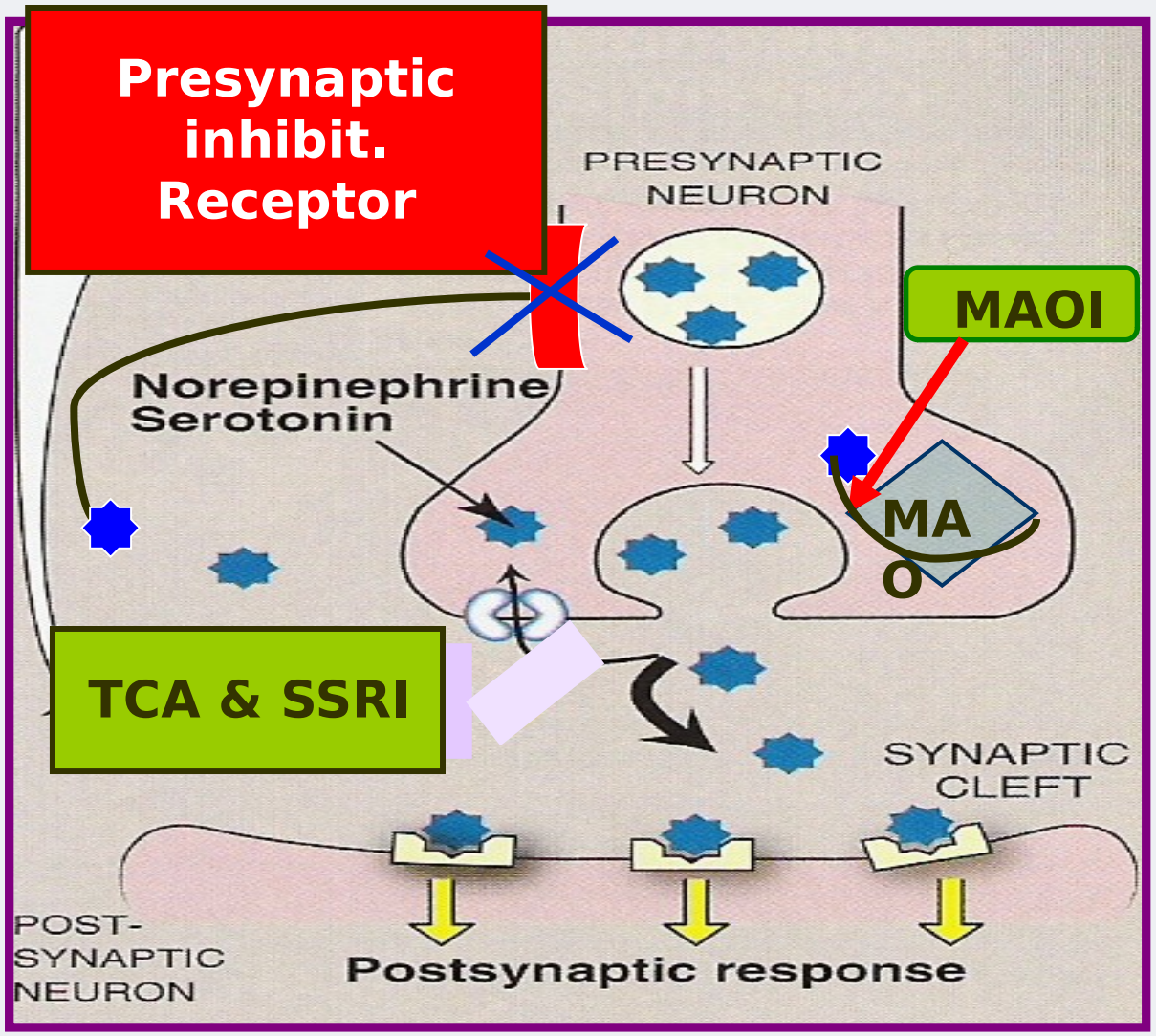
- **Depression** :

  Intense feelings of sadness, hopelessness and inability to experience pleasure in usual activities.

- **Mania**:

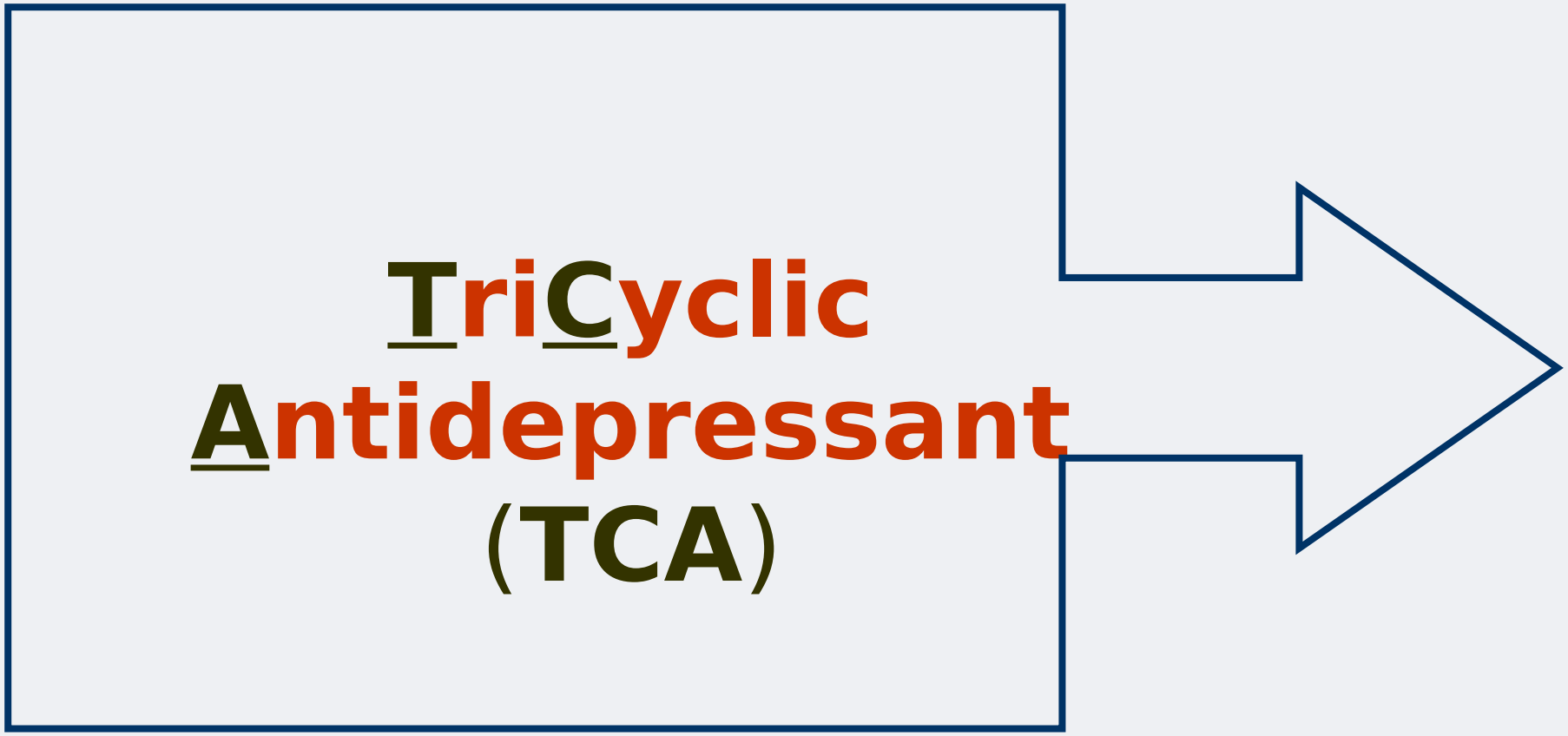
  Anger, rapid thought and speech patterns, extreme self-confidence and impaired judgment.

- **Manic-depressive illness (Bipolar disorder)**


Presynaptic inhibit. Receptor
PRESYNAPTIC NEURON
MAOI
Norepinephrine
Serotonin
MA
O
TCA & SSRI
SYNAPTIC CLEFT
POST-SYNAPTIC NEURON
Postsynaptic response

Antidepressant drugs

- TriCyclic Antidepressant (TCA)
- Mono-Amine Oxidase Inhibitors (MAOIs)
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)
- Atypical Antidepressants


TriCyclic
Antidepressant
(TCA)

TCA - Mechanism of action

1. Inhibition of neurotransmitter uptake:

- Potent **inhibitors** of the neuronal **reuptake** of **NEP & 5-HT** into presynaptic nerve terminals.

2. Blocking of receptors:

- **Block 5-HT, histaminic, α-adrenergic & muscarinic** receptors.

TCA - preparations

1- Imi/pramine the prototype drug

2- Desi/pramine

3- Ami/triptyline

4- Nor/triptyline

TCA - Actions

- **Onset of the mood elevation -- S**

TCA → **After 2-3 weeks of therapy**

- **After a therapeutic response, the dosage can be gradually reduced to improve tolerability, unless relapse occurs.**
- **Slow Withdrawal** ???????

(Physical and psychological

TCA - Therapeutic uses

- **Severe major depression.**
- **Some panic disorders (anxiety disorder)**

With sudden periods of intense fear that may include palpitations, sweating, shaking….

- **Imipramine -- to control bed-wetting**

in children (>6 years)

Cardiac arrhythmias ???????

Replaced by desmopressin

- **Amitriptyline treats neuropathic pain**

TCA - Adverse effects

- **Antimuscarinic effect** ------

  blurred vision, xerostomia (dry mouth), urinary retention, constipation, and aggravation of glaucoma.

- **Increased catecholamine activity**

  results in cardiac overstimulation that can be life-threatening if an overdose of one of the drugs is taken.

- **block α-adrenergic receptors,**

  causing orthostatic hypotension and reflex tachycardia.

Nortriptyline is **least likely** to cause:

orthostatic hypotension.

TCA - Adverse effects (cont.)

- **Sedation** during the first several weeks of treatment

  (block histamine H1 receptors)
- **Weight gain** **common adverse effect**
- **Sexual dysfunction:**

  occurs in a significant minority of patients.

Precautions:

- **in manic-depressive patients**

  (may unmask manic behavior).
- **In Patients with suicidal tendency**

--- Narrow therapeutic index (limited quantity)

Mono-Amine Oxidase Inhibitors

(MAOIs)

Mono-Amine Oxidase Inhibitors

- Two MAO Inhibitors are currently available for treatment of

  depression: **Phenelzine & Tranylcypromine**

- **Mechanism of action :**

  - irreversible inactivation of MAO ---increased stores of

  norepinephrine, serotonin, and dopamine within the neuron diffusion of excess neurotransmitters into the synaptic space

  - inhibit not only MAO enzyme in the brain but **also peripheral oxidases that catalyzes oxidative deamination of drugs & potentially toxic substances**, such as **tyramine,** which is found in

Therapeutic uses (MAOIs)

- **Depressed patients who are:**
  unresponsive or allergic to TCAs & SSRIs,
  or who experience **strong anxiety.**
- **Atypical depression:** it is characterized by **labile mood, rejection sensitivity, and appetite disorders.**
- Risk for drug-drug and drug-food **interactions** so MAOIs are considered **last-line agents** in ttt

Pharmacokinetics

- **Regeneration of enzymes occures several WKs after termination of the drug.**
- **So,when switching antidepressant agents, a minimum of 2 wks of delay must be allowed after termination of MAOIs ttt .**

Adverse effects

1) MAOIs + tyramine:

- Individuals receiving a MAOI are **unable to degrade tyramine obtained from the diet**.
- **Tyramine** causes the release of large amounts of stored catecholamines from nerve terminals, resulting in **a hypertensive crisis**
- Patients **must avoid** tyramine-containing foods.
  - **Tyramine** is contained **in foods**, such as **aged cheeses** and **meats**, **chicken liver**, **smoked fish**, and **red wines**.
- **Management of tyramine-induced hypertension**

  By: Phentolamine or prazosin

Adverse effects

2) Serotonin Syndrome:

MAOIs + SSRIs XXXX ⇒ Serotonin Syndrome

Mental status includes:

Anxiety, restlessness.

Autonomic manifestations include:

Hyperthermia,tachycardia, hypertension, vomiting, and diarrhea.

Neuromuscular hyperactivity manifest as:

Tremor, muscle rigidity, hyperreflexia.

(***Washout period of 2 WKs bet. the 2 drugs***)

In a 70-year old elderly female with depressive symptoms: Which agent would be a poor choice in this patient as the drug have significant α1 receptor antagonism and thus a higher risk for falls due to orthostatic hypotension?

A. Lithium.

B. Bupropion.

C. Fluoxitine

D. Imipramine

Selective Serotonin Reuptake Inhibitors

SSRIs

- **Specifically inhibit serotonin reuptake.**
- **Fewer adverse effects** (relatively safe)

SSRIs have little or even no blocking activity at muscarinic, α-adrenergic, and histaminic H1 receptors.

So the SSRIs have largely replaced

SSRIs - Preparations

1- Fluoxetine (Prozac) the prototype drug

2- Fluvoxamine

3- Paroxetine

- maximum benefit may require 12 WKs or more

SSRIs - Therapeutic uses

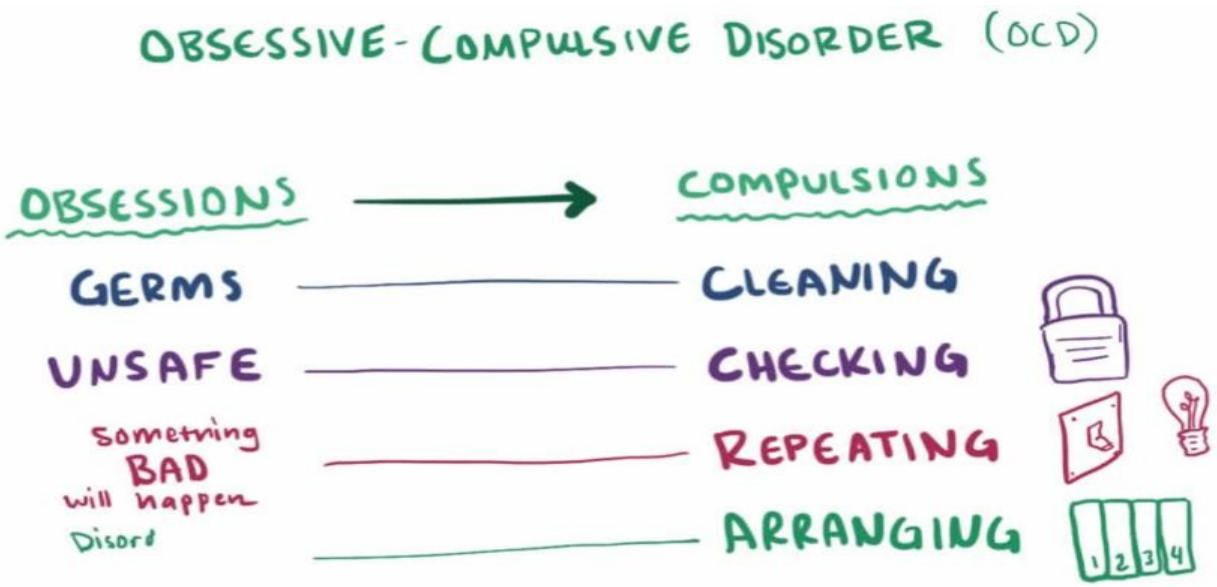
- **Depression**

  effective as the tricyclic antidepressants.
- **Obsessive compulsive disorder (the only indication for fluvoxamine)**
- **Panic disorder**
- **Generalized anxiety**
- **Premenstrual dysphoric disorder**
- **Bulimia nervosa (only Fluoxetine)**

Obsessive-Compulsive Disorder (OCD)

For Reading

Definition: a mental disorder where people have repeated and unwanted thoughts, feelings, ideas, and behaviors that drive them to do something over and over.



SSRIs - Pharmacokinetics

- **Fluoxetine:**
  - has a much longer half-life (50 hours)
  sustained release preparation (once-weekly)
  - its metabolite S- norfluoxetine is as potent as the
  parent compound & its half-life is ~ 10 days.
- **Fluoxetine and Paroxetine**
  Potent inhibitors of a hepatic cytochrome P450
  isoenzyme (CYP2D6) responsible for the elimination
  of Tricyclic antidepressant drugs, neuroleptic

SSRIs - Adverse effects

1- Nausea & anorexia ------ weight loss.

2- Sleep disturbances:

Paroxetine and **Fluvoxamine** are **sedating**.

Fatigued patients may benefit from **fluoxetine.**

(the **more activating** antidepressants)

3- Sexual dysfunction:

↓↓ the dose OR replace with a drug having fewer side effects

4- Drug interactions :

Fluoxetine and Paroxetine are potent inhibitors of a hepatic cytochrome P450

5- In children and teenagers:

should be used cautiously in children and teenagers (1:50 children become more suicidal).

6- Overdoses:

- **fluoxetine may cause seizures.**

  (up to 1200 mg compared with 20 mg/day as a therapeutic dose)

- **All SSRIs** have the potential to cause a **serotonin syndrome** when used in the presence of a **monoamine oxidase inhibitor.**

  N.B: washout period of at least 2 weeks before the other type is administered, with

SSRIs are much less effective than tricyclic antidepressants in the management of

(A) Bulimia

(B) Chronic pain of neuropathic origin

(C) Generalized anxiety disorder

(D) Obsessive-compulsive disorder

(E) Premenstrual dysphoric disorder

A 36-year-old man presents with symptoms of compulsive behavior, which is interfering with his ability to accomplish his daily tasks. Which of the following drugs would be most helpful to this patient?

A. Imipramine.

B. Fluvoxamine.

C. Amitriptyline.

D. Lithium.

Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

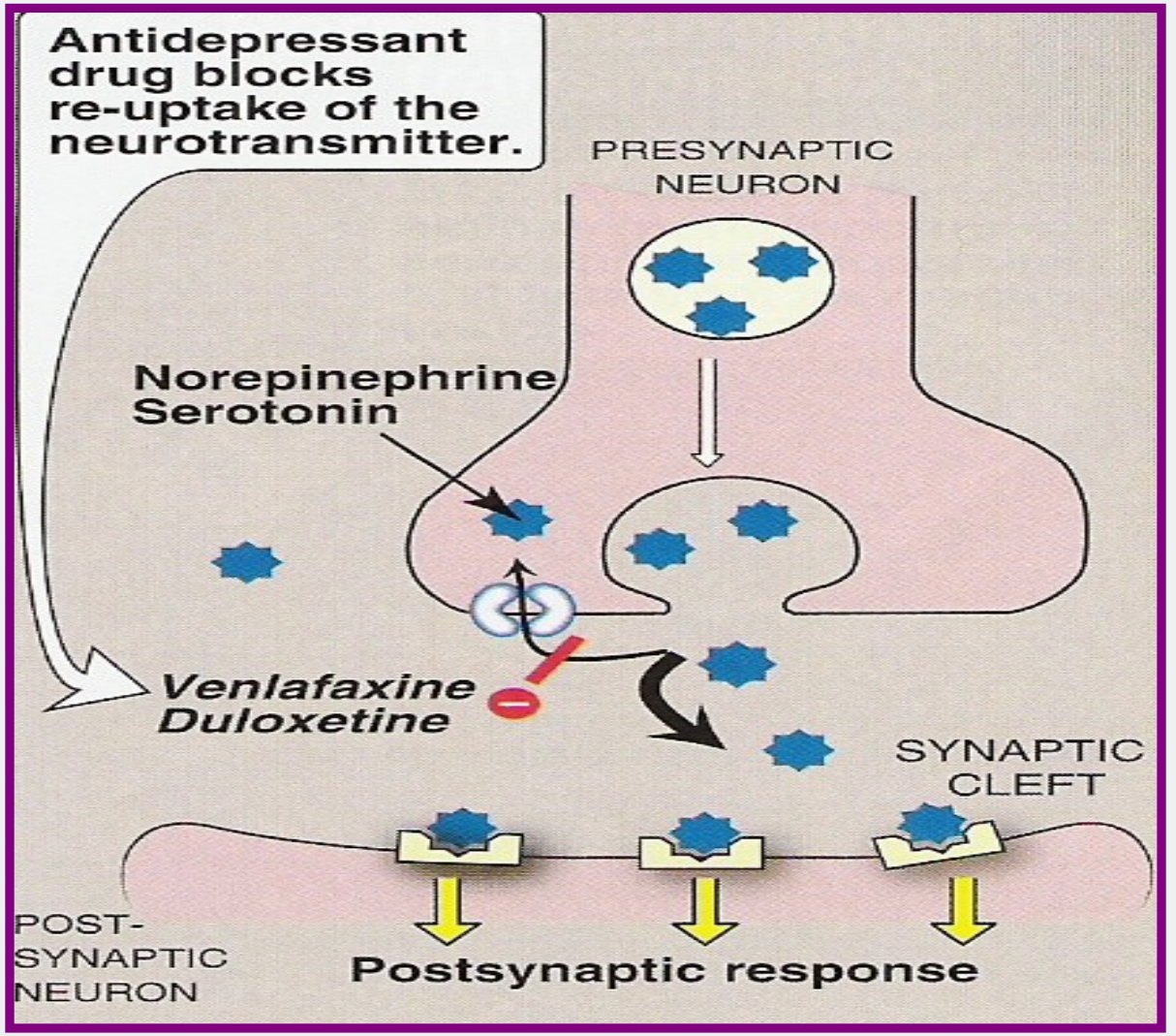
- May be effective in treating **depression** in **Patients**

  in which SSRIs are ineffective.

- SNRIs and tricyclic antidepressants, with the **dual actions of inhibiting both serotonin and norepinephrine reuptake**,

  effective in relieving neuropathic pain (e.g diabetic peripheral neuropathy, postherpetic neuralgia and low back pain).

- **SNRIs**, **unlike the TCAs**, have little activity at α-adrenergic, muscarinic, or histamine receptors and, thus,



Venlafaxine & Duloxetine

Atypical Antidepressants

- have actions at several different sites.
- not any more efficacious than the tricyclic antidepressants (TCAs) or SSRIs, but their side effect profiles are different.

Bupropion

- It is a weak dopamine and norepinephrine reuptake inhibitor that is used to **alleviate the symptoms of depression.**
- Bupropion is also useful for **decreasing cravings** and attenuating withdrawal symptoms **of nicotine** in patients trying **to quit smoking.**
- **Very low** incidence **of sexual dysfunction.**
- **low risk for drug interactions**

TREATMENT OF MANIA AND BIPOLAR DISORDER

Lithium salts

- The mode of action is unknown.
- given **orally**, and the ion is excreted by the **kidney**.
- **N.B** The antiepileptic drugs **carbamazepine** and **valproic acid** can alleviate some of the symptoms of mania.

Adverse effects

- Very toxic (extremely low therapeutic index)
- ataxia, tremors, confusion, and convulsions.
- Uncoupling of the vasopressin &TSH receptors from their G proteins

  Diabetes insipidus ---Dry mouth, polydipsia,

  and polyuria.

  Thyroid function may be decreased

Which of the following is used in patients trying to quit smoking and has a very low incidence of sexual dysfunction

A) Paroxetine

B) Fluvoxamine.

C) Bupropion.

D) Imipramine.

E) Lithium.

Which of the following is used in the treatment of bipolar disorder and may cause diabetes insipidus as a side effct?

A) Imipramine.

B) Venlafaxine

C) Fluoxetine

D) Lithium.

E) Bupropion.

Summary

TriCyclic Antidepressants:

- ✓ Potent inhibitors of the neuronal reuptake of NEP & 5-HT
- **Used in :**

Severe major depression,Some panic disorders (anxiety disorder)& treat neuropathic pain

Most important adverse effect: orthostatic hypotension& tachycardia.

Mono-Amine Oxidase Inhibitors (MAOIs):

- ✓ Act by irreversible inactivation of MAO enzymes

Most important adverse effect:

- MAOIs + tyramine tyramine-induced hypertension
- MAOIs + SSRIs Serotonin Syndrome

Selective Serotonin Reuptake Inhibitors (SSRIs):

less side effects

Used in : Depression, Panic disorder , Generalized anxiety, Premenstrual dysphoric disorder , Bulimia nervosa

NOT effective in neuropathic pain

Bupropion: weak dopamine and norepinephrine reuptake inhibitor

It is used in patients trying **to quit smoking**. It has Very Low incidence of sexual dysfunction & drug interactions

Lithium salts : treatment of mania and bipolar disorder.

Very toxic (extremely low therapeutic index)

Adverse effect: result in Diabetes insipidus & Thyroid function may be decreased

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

THAN
K YOU